CanJPsychiatry 2014;59(3):148–151

Perspective

The Mistreatment of Major Depressive Disorder

Joel Paris, MD[1]

[1] Professor of Psychiatry, McGill University, Montreal, Quebec; Research Associate, Institute of Community and Family Psychiatry, Montreal, Quebec.
Correspondence: Institute of Community and Family Psychiatry, 4333 Cote Ste Catherine, Montreal, QC H3T 1E4; joel.paris@mcgill.ca.

Key Words: depression, major depression, antidepressants

Received, revised, and accepted November 2013.

Objective: To examine the effects of classification on treatment in major depressive disorder (MDD).

Method: This is a narrative review.

Results: MDD is a highly heterogeneous category, leading to problems in classification and in specificity of treatment. Current models classify all depressions within a single category. However, the construct of MDD obscures important differences between severe disorders that require pharmacotherapy, and mild-to-moderate disorders that can respond to psychotherapy or remit spontaneously. Patients with mild-to-moderate MDD are being treated with routine or overly aggressive pharmacotherapy.

Conclusions: The current classification fails to address the heterogeneity of depression, leading to mistreatment.

Le traitement fautif du trouble dépressif majeur

Objectif : Examiner les effets de la classification sur le traitement du trouble dépressif majeur (TDM).

Méthode : Il s'agit d'une revue narrative.

Résultats : Le TDM est une catégorie hautement hétérogène, ce qui entraîne des problèmes pour la classification et la spécificité du traitement. Les modèles actuels classent toutes les dépressions dans une seule catégorie. Toutefois, le construct du TDM occulte d'importantes différences entre les troubles graves qui demandent une pharmacothérapie, et les troubles bénins à modérés qui peuvent répondre à la psychothérapie ou se rétablir spontanément. Les patients souffrant d'un TDM bénin à modéré sont traités avec la pharmacothérapie courante ou trop vigoureuse.

Conclusions : La classification actuelle ne tient pas compte de l'hétérogénéité de la dépression, ce qui entraîne un traitement fautif.

A common diagnosis in psychiatry, MDD and its treatment has long been a central concern for our specialty. However, depression can be a symptom or a syndrome, and the boundaries of depressive disorders are unclear.

Constant use over decades has reified current categories of mental disorder,[1] creating the illusion that they are established neurobiological entities. In fact, almost all are syndromes with a provisional status. While descriptive psychiatry is useful as a heuristic, it does not account for the mechanisms behind mental illness. Yet psychiatric diagnosis, encouraged by the pharmaceutical industry, has been expanded, medicalizing normal distress in a way that has been called disease-mongering.[2]

Overdiagnosis of MDD can occur in patients whose symptoms fall within other categories, or who are simply unhappy.[3] A recent large-scale survey of practice[4] found that only 38% of patients identified by clinicians as having MDD actually met formal criteria for this diagnosis, and that many received the same therapy as those who do meet criteria.[5] This is part of a larger trend, in which diagnosis-driven psychopharmacology dominates the practice of psychiatry, and in which polypharmacy has become almost routine.[6]

How Major Is Major Depressive Disorder?

The larger problem is the definition of MDD as a diagnostic category. The term major, introduced in DSM-III, and unchanged in DSM-5,[3] aims to distinguish

clinical depressions with significant effects of functioning from milder cases that are not disabling. But DSM-5 lacks a category of minor depression. While DSM-5 allows for modifiers (melancholia and psychosis), it assumes that depression is a single category, and that clinical presentations only vary according to severity. This makes MDD an overly broad and heterogeneous diagnosis. While DSM-5 specifically eschews a direct link between diagnosis and management, this classification has given clinicians the impression that all patients who meet criteria should receive the same treatment.

Considering all patients with depressive symptoms to have a single disorder also obscures etiological heterogeneity. Traditionally, psychiatrists have always made a distinction between a severe depressive illness called melancholia, and episodes of lowered mood that are primarily reactions to life circumstances.[7] Several researchers[8,9] maintain that MDD is not that major, and that melancholia should be retained as a separate category, as it has a different etiology, and because it requires different treatment.

Several decades ago, a widely quoted article in Science[10] argued that there was no basis for separate categories of depression, all of which lie on a continuum of severity. This model became highly influential, was adopted by DSM-III, and continues to appear in DSM-5,[11] in which melancholia and psychotic depression became modifiers rather than separate diagnoses.

This model can also be interpreted as suggesting that depression is a neurobiological disorder that requires pharmacological treatment—as opposed to an exaggerated response to life stressors that can respond to psychotherapy. The continued influence of the unitary model helps to explain the current tendency to treat all patients with MDD with medication. There is even a widespread perception that failure to prescribe ADs could constitute malpractice, and be the basis for a lawsuit, as indeed happened in a famous case in the United States.[12]

The division between melancholic and nonmelancholic depression is, like most distinctions in psychiatry, far from absolute. Not everyone becomes clinically depressed after a loss, and genetic vulnerability always plays a role, even in the most minor depressions.[13] Nonetheless, the evidence for a causal relation between life stressors and mild-to-moderate depression is very strong.[14] Eliminating all distinctions between the various types of depression supports treatment options that do not distinguish between conditions that respond to medication from those that do not.

Abbreviations

AD	antidepressant
AP	antipsychotic
DSM	Diagnostic and Statistical Manual of Mental Disorders
MDD	major depressive disorder

Clinical Implications

- MDD is heterogeneous.
- ADs are most effective in severe depression.
- Routine and overly aggressive psychopharmacology for mild-to-moderate depression is not based on evidence.

Limitations

- Vulnerability to depression remains poorly understood.
- More research is needed on treatments that could be specific for mild-to-moderate depression.

Which Patients Benefit From ADs?

Melancholic depression is a severe mental disorder with a strong biological component; it usually requires treatment with ADs, adjunctive APs, and (or) electroconvulsive therapy.[8] However, these treatments are less effective in mild-to-moderate depression.[15] In melancholic patients, ADs are markedly superior to placebos, which have almost no effect on the symptoms of severe depression.[16] Moreover, one of the classical characteristics of melancholia is that it comes out of the blue, and can be relatively independent of stressful circumstances.[7] In contrast, mild-to-moderate depression is best understood as an intense reaction to life stressors.[3] This distinction helps explain the findings of efficacy studies, in which the therapeutic effects of ADs depend on severity, and that in mild-to-moderate depression they rarely surpass a placebo,[16] as well as the findings of effectiveness studies,[17,18] which show that many patients do not consistently respond to AD therapy, even after augmentation and switching.

A diagnosis of MDD is not a useful guide to treatment options because the DSM-5 algorithm for diagnosis is overly inclusive. One can be categorized as having this disorder after suffering as few as 5 out of a list of 9 symptoms for as little as 2 weeks.[11] This brief time scale helps explain why the lifetime prevalence of MDD in the population is at least 50%, or even higher.[19] It also helps explain why depression screening is not particularly useful, as these procedures pick up transient and mild episodes that tend to get better on their own.[20,21]

The implication is that ADs are being overprescribed. Modern psychiatry suffers from the overselling of drugs that are effective when used for precise indications, but ineffective when prescribed for unhappiness. AD therapy would be more specific and reliable if DSM-5 had adopted a narrower definition of MDD, with criteria that specifically indicate a need for medication.

The common scenario of a poor or inadequate response to ADs has been called treatment resistance.[22] Problems in response to standard treatment have been examined in effectiveness studies that follow patients over extended periods,[18] but that design fails to control for naturalistic remission. One cannot know whether moving patients from one step to another in a research design simply allows them the time to heal on their own.

While some patients can do better on 1 AD than another, switching shows markedly diminishing returns after 2 agents have been tried.[17] Augmentation with APs presents problems because of the troubling side effects of these agents. While APs have demonstrated effectiveness in melancholia,[9] their value in mild-to-moderate depression is doubtful. The US Federal Drug Administration has accepted an indication for augmentation with some of the APs currently on the market. But this decision remains controversial, and decisions were made based on only a small number of clinical trials—all paid for by industry, and with none replicated by independent researchers.[23]

A common explanation for inconsistent response to ADs is delayed action. Many clinicians believe these agents have to be given for at least 2 weeks, or more likely for 2 months, before one can say they have not worked. Nevertheless, a large-scale meta-analysis[24] showed that patients on placebo have the same delayed response. An alternative explanation is that a percentage of treatment-resistant patients will not respond to ADs, and that some patients get better owing to naturalistic remission.

Clinicians have puzzled over the observation that some patients receiving a stable dose of ADs sometimes stop responding after a few months of treatment. While neurobiological mechanisms have been hypothesized to account for this phenomenon, it could also be explained if the populations under study are a mixture of true responders and placebo responders.[25] Given that the level of placebo response to these agents is at least 40%,[16] patients who no longer receive benefit from an AD may have only had a placebo response to begin with, or show naturalistic recovery that is attributed to a prescription. Unfortunately, placebo effects are not well understood by physicians.[26] Clinicians do not usually know whether the drugs they prescribe have worked, or whether their patients have been provided enough hope to move to a spontaneous recovery. One cannot assume that when patients feel better it proves that drugs have been effective.

Implications for the Treatment of Depression

The belief that a diagnosis of MDD is almost always an indication for prescription of ADs is a consequence of the unitary theory of depression, but is also related to the theory that mood disorders are primarily neurobiological. However, the chemical imbalances often invoked to explain clinical depression have never been shown to exist.[27] Years of propaganda from drug companies and their paid consultants from academic psychiatry have convinced clinicians that this theory is well grounded in empirical data. The reality is that we could be decades away from understanding the neural basis of diatheses for depression.

While the unitary theory downplays psychosocial factors in the etiology of depression, mild-to-moderate depression is usually related to experiences of loss that are exaggerated by diatheses. There has been a good deal of discussion of the decision by DSM-5 to eliminate the traditional exclusion when depressive symptoms appear to be causally related to grief.[28] Nevertheless, many other adverse life events (for example, losing intimate relationships or losing a job) also lead to symptoms.[29] Therefore, it is not surprising that depression does not respond in a consistent way to pharmacological treatment.

Even if it often takes longer to get results, psychotherapy, based on cognitive or on interpersonal models, is as effective as medication for milder depressions,[30] and should be considered as a first-line treatment. Unfortunately, psychiatry has moved away from an earlier interest in psychotherapy.[31] While there is little doubt that some of the earlier claims for talking cures were overblown, we have gone to the other extreme in focusing almost exclusively on psychopharmacology.[31]

Mild-to-moderate depression can be managed conservatively, without aggressive psychopharmacology. However, advocates of the unitary theory have promoted an approach poorly supported by evidence. The treatment guideline adopted by the American Psychiatric Association[32] favours immediate therapy with ADs, at any level of severity, implying that psychotherapy is less effective. In contrast, in the United Kingdom, the National Institute for Health and Care Excellence, recommends that patients with milder forms of depression should not be prescribed drugs on a first visit, but be followed supportively and encouraged to improve their lifestyle.[33] ADs are only recommended when these initial interventions fail, and psychotherapy is clearly stated to be equally effective. The Canadian Network for Mood and Anxiety Treatments guideline,[34] takes an intermediate position, suggesting that either ADs[35] or psychotherapy[36] can be first-line options.

Summary and Conclusions

Most psychiatric diagnoses describe syndromes rather than illnesses, and some are entirely based on symptoms.[31] This problem afflicts all of psychiatry, in which diagnoses are based on clinical observation, and in which researchers can only hope to identify endophenotypes.[37] Hardly any biological processes have been discovered that could be specific to any mental disorder.[38] Psychiatrists are therefore forced to fall back on clinical observation.

If response to ADs depends on severity, then medication should only be routinely prescribed when depression is either severe or shows clear-cut vegetative features, while ADs could be considered second-line options for patients who do not respond to psychotherapy.[33] Inconsistent responses to treatment can also be framed within comorbidity, as depression is a symptom that accompanies many other diagnoses. For example, patients with personality disorders do not respond well to ADs,[39] and their personality-related symptoms do not disappear when depression is treated.[40] What this tells us is that the reification of MDD fails to account for a vast heterogeneity, leading to routine treatments that sometimes work but often do not.

Instead of concerning ourselves with treatment resistance, we might consider addressing the resistance to modifying the current concept of depression. During the preparation of

DSM-5, a group of experts came out in favour of abandoning the unitary model of MDD.[41] But this suggestion was not taken up by the editors of the manual. The most likely explanation is that the unitary model has an attractive simplicity, as opposed to the more complex alternative of considering that depression is not one, but many things. When diagnostic criteria are too broad, patients can receive harm rather than benefit from treatment.[42]

Acknowledgements

Dr Paris has no conflicts of interest to declare.

References

1. Hyman S. The diagnosis of mental disorders: the problem of reification. Ann Rev Clin Psychol. 2010;6:155–179.
2. Moynihan R, Heath I, Henry D. Selling sickness: the pharmaceutical industry and disease mongering. BMJ. 2002;324:886–891.
3. Horwitz, AV, Wakefield, JC. The loss of sadness: how psychiatry transformed normal sorrow into depressive disorder. New York (NY): Oxford University Press; 2007.
4. Mojtabai R. Clinician-identified depression in community settings: concordance with structured-interview diagnoses. Psychother Psychosom. 2013;82:161–169.
5. Mojtabai R, Olfson M. Proportion of antidepressants prescribed without a psychiatric diagnosis is growing. Health Aff (Millwood). 2011;30:1434–1442.
6. Mojtabai R, Olfson M. National trends in psychotropic medication polypharmacy in office-based psychiatry. Arch Gen Psychiatry. 2010;67:26–36.
7. Berrios GE. Melancholia and depression during the 19th century. A conceptual history. Br J Psychiatry. 1988;153:298–304.
8. Parker G. Beyond major depression. Psychol Med. 2005;35:467–474.
9. Parker G. A case for reprising and redefining melancholia. Can J Psychiatry. 2013;58:183–189.
10. Akiskal HS, McKinney WT Jr. Depressive disorders: toward a unified hypothesis. Science. 1973;182:20–29.
11. American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. 5th ed. Washington (DC): APA; 2013.
12. Klerman GL. The psychiatric patient's right to effective treatment: implications of Osheroff v Chestnut Lodge. Am J Psychiatry. 1990;147:409–418.
13. Kendler KS, Neale M, Kessler RC, et al. A longitudinal twin study of personality and major depression in women. Arch Gen Psychiatry. 1993;50:853–862.
14. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. Am J Psychiatry. 1999;156:837–841.
15. Valenstein M. Keeping our eyes on STAR*D. Am J Psychiatry. 2006;193:1484–1486.
16. Kirsch I, Deacon BJ, Huedo-Medina TB, et al. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med. 2008;5:e45.
17. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA. 2010;303:47–53.
18. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med. 2006;354:1231–1242.
19. Moffitt TE, Caspi A, Taylor A, et al. How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. Psychol Med. 2009;40:899–909.
20. Patten SB. Major depression prevalence is high, but the syndrome is a poor proxy for community populations' clinical needs. Can J Psychiatry. 2008;53:411–419.
21. Thombs BD, Coyne JC, Cuijpers P, et al. Rethinking recommendations for screening for depression in primary care. CMAJ. 2012;184:413–418.
22. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am. 1996,19:179–189.
23. Paris J. The use and misuse of psychiatric drugs: an evidence-based guide. London (GB): John Wiley; 2010.
24. Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? A meta-analysis. J Clin Psychiatry. 2005;66:148–158.
25. Zimmerman M, Thongy T. How often do SSRIs and other new-generation antidepressants lose their effect during continuation treatment? Evidence suggesting the rate of true tachyphylaxis during continuation treatment is low. J Clin Psychiatry. 2007;68:1271–1276.
26. Raz A, Campbell N, Guindi D, et al. Placebos in clinical practice: a pan-Canadian review of attitudes and patterns of use between academic psychiatrists and non-psychiatrists. Can J Psychiatry. 2011;56:198–208.
27. Moncrieff J, Cohen D. How do psychiatric drugs work? BMJ. 2009;338:b1963.
28. Wakefield JC, First MB. Validity of the bereavement exclusion to major depression: does the empirical evidence support the proposal to eliminate the exclusion in DSM-5? World Psychiatry. 2012;11:3–10.
29. Wakefield JC, Schmitz MF, First MB, et al. Extending the bereavement exclusion for major depression to other losses. Arch Gen Psychiatry. 2007;64:43–440.
30. Lambert M. Bergin and Garfield's handbook of psychotherapy and behavior change. New York (NY): Wiley; 2013.
31. Paris J. Prescriptions for the mind: a critical view of contemporary psychiatry. New York (NY): Oxford University Press; 2008.
32. American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed [Internet]. Washington (DC): APA; 2010 [cited 2013 Nov 15]. Available from: http://psychiatryonline.org/content.aspx?bookid=28&sectionid=16674833.
33. National Institute for Health and Care Excellence (NICE). Depression: management of depression in primary and secondary care [Internet]. London (GB): NICE; 2009 [cited 2013 Nov 15]. Available from: http://www.nice.org.uk/nicemedia/pdf/cg90niceguideline.
34. Patten SB, Kennedy SH, Lam RW, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. I. Classification, burden and principles of management. J Affect Disord. 2009;117:S5–S14.
35. Lam RW, Grigoriadis S, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. II: pharmacotherapy. J Affect Disord. 2009;117:S26–S43.
36. Parikh SV, Segal ZV, Patten SB, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III: psychotherapy alone or in combination with antidepressant medication. J Affect Disord. 2009;117:S15–S25.
37. Gottesman I, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003;160:636–645.
38. Uher R, Rutter M. Basing psychiatric classification on scientific foundation: problems and prospects. Int Rev Psychiatry. 2012;24:591–605.
39. Newton-Howes G, Tyrer P, Johnson T. Personality disorder and the outcome of depression: meta-analysis of published studies. Br J Psychiatry. 2006;188:13–20.
40. Lopez-Castroman J, Galfalvy H, Currier D, et al. Personality disorder assessments in acute depressive episodes: stability at follow-up. J Nerv Ment Dis. 2012;200:526–530.
41. Parker G, Fink M, Akiskal H, et al. Whither melancholia? The case for its classification as a distinct mood disorder. Am J Psychiatry. 2010;167:745–767.
42. Wakefield JC, First MB. The importance and limits of harm in identifying mental disorder. Can J Psychiatry. 2013;58:618–621.